

Amendment
UISSN 10/040,319

Attorney Docket R0079C-REG

REMARKS

Amendments

Claims 1 and 10 are amended above to correct the misspelling of "substituent", and not for reasons relating to patentability. Claims 1 and 40 are additionally amended to remove matter inserted by the previous amendment to which the Examiner has objected as constituting "new matter" (e.g., matter regarding $-N=R''$ and R'''), and submit that no net diminution of claim scope results thereby.

Claim 41 (erroneously presented in the previous amendment as claim 42) is amended herein to properly depend from claim 40, as was (apparently) originally intended.

New Matter

Claims 1-16, 18-24, 26, 27, 30, 32, 34-38, and 40 were rejected under §112 as introducing new matter into the application. Applicants respectfully submit that the rejection is overcome by the above cancellation of the material to which objection was made.

Applicants agree that compounds 811 and 812 appear to be within the scope of claim 1 where $R^2 = -N=CR'-NR'R''$ (compound 811) or $(CH_2)_{0-3}-NR'R''$ (compound 812), and that the previous amendment was thus unnecessary.

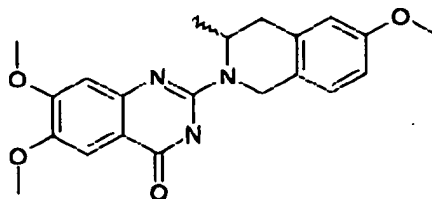
Rejection under §112, First Paragraph

A. Enablement: Claims 1-16, 18-24, 26, 27, 30, 32, 34-38, and 40 were rejected under §112, first paragraph, as lacking enablement for "individual isomers, racemic or non-racemic mixtures of isomers." Applicants respectfully traverse.

Applicants note that only a subset of the claimed compounds are optically active, as most compounds of the invention named in the specification are not optically active, possessing no chiral center. The generic formula possesses few chiral centers, particularly when R^1 is H. However, some compounds of the invention inherently possess a chiral center (for example, where R^1 is other than H, or where R^2 , R^3 , and/or R^4 include a chiral center). For example, compound 132 (page 52) has a 3-position methyl group that can have either orientation:

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Compound 132

One of ordinary skill in the art will recognize when a compound within the scope of the invention will have a chiral center. Additionally, one of skill in the art will be able to obtain either isomer or mixtures thereof by, for example, stereospecific or stereoselective synthesis or standard purification methods, such as for example, fractional crystallization employing chiral salts, HPLC using a chiral support, and the like.

With regard to the determination of relative activity or potency, Applicants note that the activity of any compound (isomer or mixture) within the scope of the invention may be determined using the methods disclosed in the specification (which are not more burdensome than other typical pharmaceutical research methods), and that it is no more difficult to test an optically active isomer than it is to test a compound lacking optical activity. Enablement within the meaning of §112 does not require Applicants to rank-order the claimed compounds by activity. Thus, Applicants respectfully submit that the claims are fully enabled.

B. Written Description: Claims 1-16, 18-24, 26, 27, 30, 32, 34-38, and 40 were rejected under §112, first paragraph, as lacking written description for "individual isomers, racemic or non-racemic mixtures of isomers." Applicants respectfully traverse.

The language "individual isomers, racemic or non-racemic mixtures of isomers" appears in the specification as filed at, inter alia, page 8, lines 3-7, page 26, lines 12-14, and isomers are discussed at page 15, line 30 to page 16, line 23. Identifying particular compounds that contain chiral centers is a trivial matter of one of ordinary skill in the art, and thus need not be pointed out in detail within the specification. Thus, Applicants submit that the presence of optical isomers and mixtures among compounds of the invention was fully recognized at the time of filing, and within the possession of the inventors.

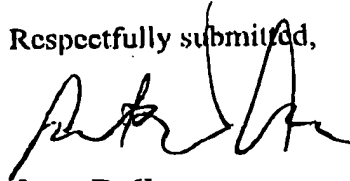
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CONCLUSION

In light of the foregoing, Applicants respectfully submit that all rejections of the pending claims have thus been overcome, and that the application has been put into condition for allowance. Applicants hereby request a Notice of Allowance for the same.

Respectfully submitted,



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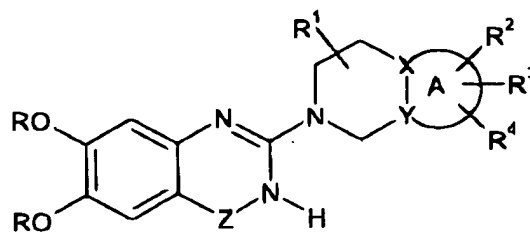
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Appendix

1. A compound comprising Formula I:



I

wherein:

X is carbon or nitrogen;

Y is carbon;

and X-Y considered together are two adjoining atoms of the ring A, said ring being a fused aromatic ring of five to six atoms per ring optionally incorporating one to two heteroatoms per ring, chosen from N, O, or S; wherein, when X is nitrogen, the bond between atoms X and Y is a single bond, and when X is carbon, the bond between atoms X and Y is double bond;

Z is -C(O)-;

each R is independently selected from lower alkyl;

R¹ is selected from:

hydrogen; lower alkyl;

aryl; arylalkyl; arylaminocarbonyl; wherein the aryl group is optionally substituted with one to two substituents selected from lower alkyl, halo, cyano and lower alkoxy; and

heteroaryl or heteroarylalkyl, wherein the aryl group is optionally substituted with one or two substituents selected from the group consisting of lower alkyl, halogen, cyano, and lower alkyl;

R², R³, and R⁴ are each independently in each occurrence selected from:

hydrogen; lower alkyl;

cycloalkyl or cycloalkylalkyl, wherein the cycloalkyl group is optionally substituted with one, two, or three substituents selected from the group consisting of

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hydroxy, cyano, lower alkyl, lower alkoxy, halo-lower alkoxy, alkylthio, halogen, haloalkyl, hydroxyalkyl, nitro, alkoxycarbonyl, amino, alkylamino, alkylsulfonyl, arylsulfonyl, alkylaminosulfonyl, arylaminosulfonyl, alkylsulfonylamino, arylsulfonylamino, alkylaminocarbonyl, arylaminocarbonyl, alkylcarbonylamino, arylcarbonylamino, and phenyl optionally substituted with one or two substituents selected from the group consisting of lower alkyl, halogen, cyano and lower alkoxy;

aryl or arylalkyl, wherein the aryl group is optionally substituted with one, two, or three substituents selected from the group consisting of hydroxy, cyano, lower alkyl, lower alkoxy, halogen-lower alkoxy, alkylthio, halogen, haloalkyl, hydroxyalkyl, nitro, alkoxycarbonyl, amino, alkylamino, alkylsulfonyl, arylsulfonyl, alkylaminosulfonyl, arylaminosulfonyl, alkylsulfonylamino, arylsulfonylamino, alkylaminocarbonyl, arylaminocarbonyl, alkylcarbonylamino, and arylcarbonylamino, or two adjacent atoms of the aryl ring can be substituted with a methylenedioxy or ethylenedioxy group to form a fused heterocyclyl ring;

heterocyclyl or heterocyclylalkyl, wherein the heterocyclyl group is optionally substituted with one, two, or three substituents selected from the group consisting of hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, lower alkyl, lower alkoxy, alkoxyalkyl, halogen-lower alkoxy, alkylthio, halogen, haloalkyl, nitro, alkoxycarbonyl, amino, alkylamino, alkylsulfonyl, arylsulfonyl, alkylaminosulfonyl, arylaminosulfonyl, alkylsulfonylamino, arylsulfonylamino, alkylaminocarbonyl, arylaminocarbonyl, alkylcarbonylamino, arylcarbonylamino, and phenyl optionally substituted with one or two substituents selected from the group consisting of lower alkyl, halogen, cyano and lower alkoxy;

heteroaryl or heteroarylalkyl, wherein the heteroaryl group is optionally substituted with one, two, or three substituents selected from the group consisting of hydroxy, cyano, lower alkyl, lower alkoxy, halogen-lower alkoxy, alkylthio, halogen, haloalkyl, hydroxyalkyl, nitro, alkoxycarbonyl, amino, alkylamino,

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alkylsulfonyl, arylsulfonyl, alkylaminosulfonyl, arylaminosulfonyl,
alkylsulfonylamino, arylsulfonylamino, alkylaminocarbonyl,
arylaminocarbonyl, alkylcarbonylamino, and arylcarbonylamino;
hydroxy; hydroxyalkyl; alkoxy; alkoxyalkyl;
halo; haloalkyl; cyano; cyanoalkyl; and
-(CH₂)₀₋₃NR'R"; -C(=N)-NR'R"; -N-C(-NR')-R"; -N=CR'-NR'R"; -SO₂NR'R";
-NSO₂R'; -C(O)R'; -C(O)NR'R"; or -NC(O)R';

with the proviso that if A is a benzene ring, at least one of R², R³ or R⁴ is not
hydrogen; or

R² and R³, if adjacent, taken together with the carbons to which they are attached may form
a 5- to 7- membered aromatic, saturated or unsaturated ring, optionally incorporating
one or two ring heteroatoms chosen from N, S, or O, which can be optionally
substituted with one or two substituents selected from lower alkyl, halo, haloalkyl,
cyano, alkylthio, and lower alkoxy; and

R' and R" are independently in each occurrence selected from:

hydrogen; lower alkyl; substituted lower alkyl;

hydroxyalkyl; alkoxyalkyl;

cycloalkyl, wherein the cycloalkyl group is optionally substituted with one, two, or
three substituents selected from the group consisting of hydroxy, cyano,
lower alkyl, lower alkoxy, halogen-lower alkoxy, alkylthio, halogen,
haloalkyl, hydroxyalkyl, nitro, alkoxycarbonyl, amino, alkylamino,
alkylsulfonyl, arylsulfonyl, alkylaminosulfonyl, arylaminosulfonyl,
alkylsulfonylamino, arylsulfonylamino, alkylaminocarbonyl,
arylaminocarbonyl, alkylcarbonylamino, arylcarbonylamino, and phenyl;

aryl or arylalkyl, wherein the aryl group is optionally substituted with one, two, or
three substituents selected from the group consisting of hydroxy, cyano,
lower alkyl, lower alkoxy, halogen-lower alkoxy, alkylthio, halogen,
haloalkyl, hydroxyalkyl, nitro, alkoxycarbonyl, amino, alkylamino,
alkylsulfonyl, arylsulfonyl, alkylaminosulfonyl, arylaminosulfonyl,
alkylsulfonylamino, arylsulfonylamino, alkylaminocarbonyl,

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arylamincarbonyl, alkylcarbonylamino, and arylcarbonylamino, or two adjacent atoms of the aryl ring can be substituted with a methylenedioxy or ethylenedioxy group to form a fused heterocyclic ring;

heteroaryl or heteroarylalkyl, wherein the heteroaryl group is optionally substituted with one, two, or three substituents selected from the group consisting of hydroxy, cyano, lower alkyl, lower alkoxy, halogen-lower alkoxy, alkylthio, halogen, haloalkyl, hydroxyalkyl, nitro, alkoxycarbonyl, amino, alkylamino, alkylsulfonyl, arylsulfonyl, alkylaminosulfonyl, arylaminosulfonyl, alkylsulfonylamino, arylsulfonylamino, alkylaminocarbonyl, arylaminocarbonyl, alkylcarbonylamino, and arylcarbonylamino;

heterocyclyl or heterocyclylalkyl, wherein the heterocyclyl group is optionally substituted with one, two, or three substituents selected from the group consisting of hydroxy, oxo, cyano, cyanoalkyl, lower alkyl, lower alkoxy, halogen-lower alkoxy, alkylthio, halogen, haloalkyl, hydroxyalkyl, nitro, alkoxycarbonyl, amino, alkylamino, alkylsulfonyl, arylsulfonyl, alkylaminosulfonyl, arylaminosulfonyl, alkylsulfonylamino, arylsulfonylamino, alkylaminocarbonyl, arylaminocarbonyl, alkylcarbonylamino, and arylcarbonylamino;

or R' and R" together with the nitrogen to which they are attached may form a 5- to 7-membered ring, optionally incorporating one additional ring heteroatom chosen from N, O or S; wherein this ring is optionally substituted with one or two substituents selected from the group consisting of lower alkyl, halogen, cyano, lower alkoxy and phenyl optionally substituted with one or two substituents selected from the group consisting of lower alkyl, halogen, cyano and lower alkoxy;

or individual isomers, racemic or non-racemic mixtures of isomers or pharmaceutically acceptable salts or solvates thereof.

2. The compound of Claim 1, wherein X is carbon.
3. The compound of Claim 1, wherein X is nitrogen.

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4. The compound of Claim 1, wherein R^1 is hydrogen.
5. The compound of Claim 4, wherein X is carbon and A is a fused aryl ring.
6. The compound of Claim 5, wherein A is a fused benzene ring.
7. The compound of Claim 4, wherein X is carbon and A is a fused heteroaryl ring.
8. The compound of Claim 7, wherein A is a fused pyrimidine ring.
9. The compound of Claim 7, wherein A is a fused pyrrole ring.
10. The compound of Claim 9, wherein R^2 and R^3 taken together with the carbons to which they are attached form a fused benzene ring, optionally substituted with one or two substituents selected from lower alkyl, halo, haloalkyl, cyano, alkylthio, or lower alkoxy.
11. The compound of Claim 7, wherein A is a fused pyridine ring.
12. The compound of Claim 7, wherein A is a fused imidazole ring.
13. The compound of Claim 4, wherein X is nitrogen and A is a fused imidazole ring.
14. The compound of Claim 4, wherein R^2 is $-(CH_2)_{0-3}NR'R''$ or $-SO_2NR'R''$, and wherein R' and R'' are independently in each occurrence selected from hydrogen, lower alkyl, substituted lower alkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, or R' and R'' together with the nitrogen to which they are attached may form a 5- to 7- membered ring, optionally incorporating one additional ring heteroatom chosen from N, O, or S.

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15. The compound of Claim 6, wherein R^2 is $-(CH_2)_{0-3}NR'R''$ or $-SO_2NR'R''$, and wherein R' and R'' are independently in each occurrence selected from hydrogen, lower alkyl, substituted lower alkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, or R' and R'' together with the nitrogen to which they are attached may form a 5- to 7- membered ring, optionally incorporating one additional ring heteroatom chosen from N, O, or S.

16. The compound of Claim 15, wherein Z is $-C(O)-$.

17. (Canceled).

18. The compound of Claim 6, wherein R^2 is selected from the groups $-C(NH)-NR'R''$, $-N-C(NR')-R''$, and $-N=CR'-NR'R''$, and wherein R' and R'' are independently in each occurrence selected from hydrogen, lower alkyl, substituted lower alkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, or R' and R'' together with the nitrogen to which they are attached may form a 5- to 7- membered ring, optionally incorporating one additional ring heteroatom chosen from N, O, or S.

19. The compound of Claim 18, wherein Z is $-C(O)-$.

20. A compound of Claim 6, wherein R^2 is aryl or heteroaryl.

21. A compound of Claim 6, wherein R^2 is alkoxy, cyano, or cyanoalkyl.

22. The compound of Claim 8, wherein R^2 is $-(CH_2)_{0-3}NR'R''$ or $-SO_2NR'R''$, and wherein R' and R'' are independently in each occurrence selected from hydrogen, lower alkyl, substituted lower alkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, or R' and R'' together with the nitrogen to which they are attached may form a 5- to 7- membered ring, optionally incorporating one additional ring heteroatom chosen from N, O, or S.

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23. The compound of Claim 22, wherein R^2 is $-NR'R''$, and wherein R' and R'' are selected from hydrogen or alkyl, or R' and R'' taken together with the nitrogen to which they are attached may form a 5- to 7- membered ring, optionally incorporating one additional ring heteroatom chosen from N, O, or S.
24. The compound of Claim 22, wherein Z is $-C(O)-$.
25. (canceled).
26. The compound of Claim 13, wherein R^2 is $-(CH_2)_{0-3}NR'R''$ or $-SO_2NR'R''$, and wherein R' and R'' are independently in each occurrence selected from hydrogen, lower alkyl, substituted lower alkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, or R' and R'' together with the nitrogen to which they are attached may form a 5- to 7- membered ring, optionally incorporating one additional ring heteroatom chosen from N, O or S.
27. The compound of Claim 26, wherein Z is $-C(O)-$.
28. (Canceled).
29. The compound of Claim 1, wherein the compound is:
6,7-dimethoxy-2-[5-(4-methoxy-phenyl)-3,4-dihydro-1H-isoquinolin-2-yl]-3H-quinazolin-4-one;
6,7-dimethoxy-2-[7-(4-methoxy-phenyl)-3,4-dihydro-1H-isoquinolin-2-yl]-3H-quinazolin-4-one;
6,7-dimethoxy-2-(4-morpholin-4-yl-5,8-dihydro-6H-pyrido[3,4-d]pyrimidin-7-yl)-3H-quinazolin-4-one;
6,7-dimethoxy-2-(5-pyridin-3-yl-3,4-dihydro-1H-isoquinolin-2-yl)-3H-quinazolin-4-one;
2-(4-benzylamino-5,8-dihydro-6H-pyrido[3,4-d]pyrimidin-7-yl)-6,7-dimethoxy-3H-quinazolin-4-one;
6,7-dimethoxy-2-(5-pyrrolidin-1-yl-3,4-dihydro-1H-isoquinolin-2-yl)-3H-quinazolin-4-one;

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6,7-dimethoxy-2-(5-pyridin-4-yl-3,4-dihydro-1*II*-isoquinolin-2-yl)-3*H*-quinazolin-4-one;
6,7-dimethoxy-2-(5-pyrimidin-5-yl-3,4-dihydro-1*H*-isoquinolin-2-yl)-3*H*-quinazolin-4-one;
2-(6,7-dimethoxy-4-oxo-1,4-dihydro-quinazolin-2-yl)-1,2,3,4-tetrahydro-isoquinoline-7-sulfonic acid (2-pyridin-2-yl-ethyl)-amide;
2-(6,7-dimethoxy-4-oxo-3,4-dihydro-quinazolin-2-yl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline-5-carbonitrile;
6,7-dimethoxy-2-[5-(1*H*-pyrrol-2-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-3*II*-quinazolin-4-one;
2-[5-(1*II*-imidazol-2-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-6,7-dimethoxy-3*H*-quinazolin-4-one;
6,7-dimethoxy-2-[4-(4-methyl-piperazin-1-yl)-5,8-dihydro-6*II*-pyrido[3,4-*d*]pyrimidin-7-yl]-3*II*-quinazolin-4-one;
6,7-dimethoxy-2-{4-[(2-methoxy-ethyl)-methyl-amino]-5,8-dihydro-6*II*-pyrido[3,4-*d*-pyrimidin-7-yl]}-3*H*-quinazolin-4-one;
6,7-dimethoxy-2-[5-(morpholine-4-sulfonyl)-3,4-dihydro-1*II*-isoquinolin-2-yl]-3*H*-quinazolin-4-one;
6,7-dimethoxy-2-(4-piperidin-1-yl-5,8-dihydro-6*II*-pyrido[3,4-*d*]pyrimidin-7-yl)-3*H*-quinazolin-4-one;
6,7-dimethoxy-2-[5-(1-morpholin-4-yl-methanoyl)-3,4-dihydro-3*H*-isoquinolin-2-yl]-3*II*-quinazolin-4-one;
6,7-dimethoxy-2-(1-phenyl-1,4,6,7-tetrahydro-imidazo[4,5-*c*]pyridin-5-yl)-3*H*-quinazolin-4-one;
2-[1-(4-chloro-phenyl)-1,4,6,7-tetrahydro-imidazo[4,5-*c*]pyridin-5-yl]-6,7-dimethoxy-3*H*-quinazolin-4-one;
6,7-dimethoxy-2-(1-naphthalen-2-yl-1,4,6,7-tetrahydro-imidazo[4,5-*c*]pyridin-5-yl)-3*H*-quinazolin-4-one;
6,7-dimethoxy-2-[1-(4-methoxy-phenyl)-1,4,6,7-tetrahydro-imidazo[4,5-*c*]pyridin-5-yl]-3*II*-quinazolin-4-one;
2-[1-(3-chloro-phenyl)-1,4,6,7-tetrahydro-imidazo[4,5-*c*]pyridin-5-yl]-6,7-dimethoxy-3*H*-quinazolin-4-one;

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6,7-dimethoxy-2-(1-*m*-tolyl-1,4,6,7-tetrahydro-imidazo[4,5-*c*]pyridin-5-yl)-3*II*-quinazolin-4-one;

6,7-dimethoxy-2-(3-phenyl-5,6-dihydro-8*H*-imidazo[1,5-*a*]pyrazin-7-yl)-1*H*-quinazolin-4-one;

2-(3-cyclohexyl-5,6-dihydro-8*II*-imidazo[1,5-*a*]pyrazin-7-yl)-6,7-dimethoxy-1*H*-quinazolin-4-one;

6,7-dimethoxy-2-(1,3,4,9-tetrahydro- β -carbolin-2-yl)-3*H*-quinazolin-4-one;

6,7-dimethoxy-2-(6-methoxy-1,3,4,9-tetrahydro- β -carbolin-2-yl)-3*H*-quinazolin-4-one;

6,7-dimethoxy-2-(7-methylsulfanyl-1,3,4,9-tetrahydro- β -carbolin-2-yl)-3*H*-quinazolin-4-one;

2-(3,4-dihydro-1*II*-2,7,10-triaza-anthracen-2-yl)-6,7-dimethoxy-3*H*-quinazolin-4-one;

N-[2-(6,7-dimethoxy-4-oxo-3,4-dihydro-quinazolin-2-yl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-cyclopentanecarboxamidine;

6,7-dimethoxy-2-(5-morpholin-4-ylmethyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-3*II*-quinazolin-4-one;

6,7-dimethoxy-2-(5-piperidin-1-ylmethyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-3*H*-quinazolin-4-one;

2-[5-(4,5-dihydro-1*II*-imidazol-2-ylamino)-3,4-dihydro-1*II*-isoquinolin-2-yl]-6,7-dimethoxy-3*II*-quinazolin-4-one;

N-[2-(6,7-dimethoxy-4-oxo-3,4-dihydro-quinazolin-2-yl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-cyclobutanecarboxamidine;

N-[2-(6,7-dimethoxy-4-oxo-3,4-dihydro-quinazolin-2-yl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-butyramidine;

N-[2-(6,7-dimethoxy-4-oxo-3,4-dihydro-quinazolin-2-yl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-*N,N*-dimethyl-formamidine;

6,7-dimethoxy-2-[5-(1-methyl-4,5-dihydro-3*II*-pyrrol-2-ylamino)-3,4-dihydro-1*H*-isoquinolin-2-yl]-3*H*-quinazolin-4-one; or

2-[5-(4,5-dihydro-3*H*-pyrrol-2-ylamino)-3,4-dihydro-1*H*-isoquinolin-2-yl]-6,7-dimethoxy-3*H*-quinazolin-4-one; or a pharmaceutically-acceptable salt thereof.

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30. A pharmaceutical composition comprising a therapeutically effective amount of at least one compound of Claim 1 in admixture with at least one pharmaceutically acceptable carrier.

31. (Canceled)

32. A method of treating a subject having a disease state that is alleviated by treatment with an alpha-1A/1B adrenoceptor antagonist, which method comprises administering to the subject a therapeutically effective amount of at least one compound of Claim 1.

33. (Canceled)

34. The method of Claim 32 wherein the disease state comprises disorders and symptoms of the urinary tract.

35. The method of Claim 32 wherein the disease state comprises improvement of sexual dysfunction.

36. The method of Claim 32 wherein the disease state comprises benign prostatic hypertrophy and the irritative symptoms associated with benign prostatic hypertrophy.

37. The method of Claim 32 wherein the disease state comprises pain.

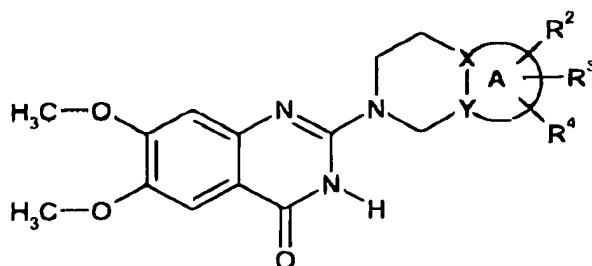
38. The method of Claim 37 wherein the disease state comprises inflammatory pain, neuropathic pain, cancer pain, acute pain, chronic pain, or complex regional pain syndromes.

39. (Canceled)

40. A compound having the formula,

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wherein:

X is carbon or nitrogen;

Y is carbon; and X-Y considered together are two adjoining atoms of the ring A, said ring being selected from a fused benzo, pyrrolyl, imidazolyl, pyridyl, or pyrimidinyl ring; wherein when X is nitrogen, the bond between atoms X and Y is a single bond, and when X is carbon, the bond between atoms X and Y is double bond; and

R², R³, and R⁴ are each independently in each occurrence selected from:

hydrogen; lower alkyl;

hydroxy; hydroxyalkyl; alkoxy; alkoxyalkyl;

halo; haloalkyl; cyano; cyanoalkyl;

cyclopentyl, cyclohexyl, or cycloheptyl;

phenyl, phenyl(lower alkyl), pyridyl, pyridyl(lower alkyl) pyrimidinyl,

pyrimidinyl(lower alkyl), pyrazinyl, pyrazinyl (lower alkyl), pyrrolyl,

pyrrolyl(lower alkyl), imidazolyl, imidazolyl(lower alkyl), and naphthyl, each

of said aryl and heteroaryl rings in turn optionally substituted with one to two

halogen, lower alkoxy, lower alkyl, trifluoromethyl, methylthiol, and/or

amino;

morpholinyl, morpholinyl(lower alkyl), piperidinyl, piperidinyl(lower alkyl),

piperazinyl, piperazinyl(lower alkyl) pyrrolidinyl, pyrrolidinyl(lower alkyl),

imidazolidinyl, imidazolidinyl(lower alkyl), tetrahydrofuryl,

tetrahydrofuryl(lower alkyl), and 1-H-pyrimidine-2,4-dione, each of said

heterocyclic rings in turn optionally substituted with one to two of hydroxy,

oxo, lower alkoxy, hydroxy(lower alkyl), and/or phenyl, said phenyl in turn

optionally substituted with one or two substituents selected from the group

consisting of lower alkyl, halogen, cyano and lower alkoxy;

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$-(CH_2)_{0-3}NR'R''$; $-SO_2NR'R''$; $-C(O)R'$; $-C(=NH)-NR'R''$; $-N-C(-NH)-R''$; and
 $-N-CR'-NR'R''$;

or R^2 and R^3 taken together form a fused pyridyl or a methylenedioxy or ethylenedioxy group to form a fused heterocyclic ring;

with the proviso that if A is a benzene ring, at least one of R^2 , R^3 or R^4 is not hydrogen;

R and R'' are individually selected from hydrogen, lower alkyl, lower alkoxy, hydroxyalkyl, phenyl, phenyl(lower alkyl), pyridyl, pyridyl(lower alkyl), pyrrolidinyl, furyl, imidazolidinyl, piperidinyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, morpholinyl, said rings in turn optionally substituted with lower alkyl, lower alkoxy, cyano(lower alkyl), 5,6-dihydro-2H-thiazin-3-yl;

or alternatively, R' and R'' together with the nitrogen to which they are attached may form a piperidinyl or morpholinyl ring optionally substituted with one or two substituents selected from the group consisting of lower alkyl, lower alkoxy, cyano, or cyano(lower alkyl).

41. A compound according to claim 40, in which X is carbon and A is a fused aryl, pyridyl, or pyrimidinyl ring.